and

(B) each of said protein and said fragment raises antibody suitable for immunohistochemical staining of cancerous human tissue.

19. The polypeptide of claim 18, wherein said polypeptide is human autotaxin protein.

20. The polypeptide of claim 19, wherein said human autotaxin protein has the amino acid sequence of an autotaxin protein isolated from human A2508 melanoma cells.

21. The polypeptide of claim 18, wherein said polypeptide is a fragment of said human autotaxin protein.

22. The polypeptide of claim 21, wherein said fragment contains an amino acid sequence selected from the group consisting of SEQ ID Nos. 1-11 and 26-33.

REMARKS

Pursuant to the present amendment, claims 3-6 and 16-17 have been canceled and claims 18-22 have been added to recite applicants' claimed invention more clearly. Claim 18 roughly corresponds to canceled claim 3, claim 20 to canceled claim 16, and claim 22 to canceled claim 4. The specification has been amended to correct a typographical error on page 35 that erroneously correlates SEQ ID NO:10 to ATX-101. Support for this amendment can be found at page 33, line 14, of the original specification where SEQ ID NO:10 is shown to correspond to ATX-102.

As prescribed in new claim 18, applicants have discovered a new protein, autotaxin, which has a molecular weight of about

125 kDa and an isoelectric point of about 7.7, and which displays motility inducing activity. This protein and fragments of it raise antibody suitable for immunohistochemical staining of cancerous human tissue. Support for recitations pertaining to these features of applicants' invention can be found, for example, at pages 11, 15, and 30 of the original specification.

Since the new claims are fully supported in the original application, the present amendment introduces no new matter. Applicants therefore request that Examiner Celsa enter the above-discussed revisions and reconsider the pending action in light of the following remarks.

35 USC §102(b) Rejections

Claims 3 and 16 stand rejected under 35 USC §102(b) over Liotta *et al*. Applicants would emphasize, however, that Liotta's disclosures relating to an autocrine motility factor associated with human A2058 melanoma cells does not anticipate the claimed polypeptides. Liotta discloses a motility factor with an estimated size of 55 kDa, which is less than half the size of autotaxin (125 kDa). The molecular weight of autotaxin has been confirmed by direct protein staining of polyacrylamide gels, as well as by immunoblot of partially purified protein using antipeptide antibody to identify autotaxin. Additionally, the chromatographic separation methodology used to purify autotaxin fails to co-purify a 55 kDa protein. Yet, if AMF and autotaxin were the same, or if AMF was a fragment of autotaxin, one would expect the separation methodology to purify both autotaxin and AMF.

The amino acid composition of AMF, shown in Table 2 of the article, is quite different from the amino acid composition of autotaxin (see page 31 of the application). The molecular weight of autotaxin after deglycosylation is 100 kDa, indicating that

it contains about 900 amino acid residues, including 63 glycine and 51 serine residues. In contrast, AMF is expected to have about 500 amino acid residues, including 118 glycine residues and 62 serine residues. Thus, while AMF is smaller than autotaxin it has more glycine and serine residues than autotaxin, and thus is different from autotaxin. Furthermore, as stated at pages 4-5 of the instant specification, no significant degree of homology was found between autotaxin and previously disclosed motility factors, including AMF.

Additionally, applicants have raised three different antibodies against autotaxin that failed to recognize a 55 kDa peptide. Also, while the activity of autotaxin is lost when it is exposed to a pH of <6, AMF loses activity at a pH of ≤4. Accordingly, autotaxin "is unique from any previously identified or purified motility factor" (specification at page 4).

Applicants can submit a declaration attesting to these differences between AMF and autotaxin, if Examiner Celsa believes that such a declaration would advance the prosecution of this application. In the meantime, the newly presented claims specifically recite features of the instant invention that distinguish it from Liotta. For example, the molecular weight of the claimed protein is recited to be about 125 kDa. These claims are clearly patentable over the Liotta teachings, and reconsideration and withdrawal of this rejection therefore are respectfully requested.

35 USC §103 Rejections

Claims 5 and 17 are rejected as obvious over Liotta in view of Yarmush *et al*. This §103 rejection is traversed for the reasons set forth above. Since Liotta *et al*. do not anticipate or suggest the claimed polypeptide, no combination of Liotta with a reference teaching a polypeptide bound to a solid support could

render applicants' invention obvious within the meaning of §103. In any event, applicants' cancellation of the rejected claims renders the rejection moot.

35 USC §101 Rejections

The examiner has rejected claims 3-6 and 16-17 under 35 USC §101 on the grounds that they (i) are directed to non-statutory subject matter and (ii) are not "useful" within the meaning of the statute.

Ground (i) may arise from a misreading of the rejected claims. The examiner has said that applicants are claiming a "polypeptide which is naturally associated with proteins." Yet the claims prescribe precisely the opposite, namely, that the "polypeptide" in question is "**free** of proteins with which it is **naturally associated**" (emphasis added). Such a polypeptide is clearly not in a form that is found in nature.

In an attempt to clarify this matter, applicants now present claims that recite human autotaxin protein in homogeneous form, which also is not a product of nature. Reconsideration therefore is requested for this aspect of the examiner's stated rationale for rejection.

As to ground (ii), the examiner contends that applicants have not shown all of the claimed peptides to be useful "in therapeutic and diagnosis of cancer," and that applicants' invention is "speculative in nature." Applicants traverse this rejection because the specification provides ample support for the utility of the claimed invention.

In particular, page 13 of the specification discloses that "antibodies can be raised to autotaxin or its fragment peptides," while page 15 states that antibodies to autotaxin can be used,

for example, in "ELISA, RIA or immunoblots configurations," and "can also be used in immunostains." These express teachings of a usefulness for the claimed invention in diagnosing cancer must be accepted by the PTO, absent evidence or reasoning to the contrary. Notably, the examiner has identified no such contradicting evidence or reasoning ***with respect to the described diagnostic utility***.

Furthermore, Example 5 at page 35 of the specification demonstrates an actual use of an autotaxin fragment peptide, ATX-102 (SEQ ID NO:10). More specifically, ATX-102 was used to raise antibody that recognizes autotaxin on immunoblots and that "has been used to perform immunohistochemical stains on human tissue." While the law does not require working examples to "demonstrate" utility, applicants thus have provided an example of the claimed invention in actual use.

In the same vein, Applicants also provide as APPENDIX A to this response, an immunoblot which shows that the antibody disclosed in Example 5 recognizes autotaxin. Lane 1 contains protein molecular weight standards and lanes 2 and 3 contain partially purified autotaxin separated by polyacrylamide gel electrophoresis and electrophoretically transferred to Immobilon™. In lane 2, the antipeptide antibody is seen to react with a 125 kDa protein. In lane 3, this reaction is inhibited by adding excess peptide (100-fold molar excess). This immunoblot demonstrates that the antibody has specificity for autotaxin. Applicants also have determined that, when this antibody is used for immunoperoxidase staining of human tumor tissue, the antibody is shown preferentially to stain the tumor tissue and not the normal host tissue. Again, applicants would be happy to provide these data to the examiner in the form of a declaration attesting to the utility of the claimed invention.

The examiner also contends that applicants have not demonstrated the utility of the claimed fragments because they have not identified the primary, secondary, tertiary and quaternary structure of the protein. Applicants would emphasize, however, that information concerning "the structure of the protein necessary for the protein's biological activity" is not necessary to establish an "activity correlatable to diagnosing ... cancer." Furthermore, as discussed in the foregoing paragraph, applicants have indeed "provided data supporting such activity."

Based on the foregoing, applicants submit that the examiner's §101 rejection lacks substantive foundation and should be withdrawn. Reconsideration by the examiner therefore is respectfully requested.

Rejections Under 35 USC §112, First Paragraph

The examiner has objected to the specification for failing to enable a method for using the claimed polypeptides "either diagnostically or therapeutically to treat cancer" (emphasis added). But while stating, without supportive citation, that "the treatment of cancer is highly unpredictable," the examiner says nothing at all about ***diagnosis*** in the present context, notwithstanding applicants' express teachings relevant to a method for using for their invention diagnostically. Applicants further note that no principle of §112 requires them to provide examples or "extensive clinical data."

In any event, applicants have demonstrated the use of the claimed invention in diagnosing cancer (see, for example, pages 13 and 15 of the specification). Applicants therefore must protest the examiner's characterization of the teachings set forth on pages 13-16 of the application as merely "speculative." These teachings are sufficient to allow one skilled in the

relevant art to use the claimed invention in diagnosing cancer. Furthermore, applicants have provided a working example of the use of an autotaxin fragment in diagnosing cancer (specification at page 35). Thus, contrary to the examiner's assertion, applicants indeed have enabled a method of using the claimed polypeptides. Applicants respectfully request that Examiner Celsa reconsider and withdraw this objection.

The examiner also has argued that applicants have failed adequately to describe peptides that have "X" (potentially glycosylated) amino acid residues. As shown on page 33 of the specification, however, peptide 5 (SEQ ID NO:5) and peptide 17 (SEQ ID NO:31) indeed are such peptides. According to standard practice in the art, "X" is used to describe unknown amino acids encountered during the course of peptide sequence analysis. For example, amino acids which have attached sugar moieties do not sequence well during standard sequencing techniques. The most commonly glycosylated residues are asparagine, serine, and threonine. It is likely that each of the "X" residues in the autotaxin peptides are one of these three amino acids. Absent any elaboration by the examiner as to a rationale for his objection, applicants can say only that the peptides in question are "adequately described," and they request withdrawal of this objection.

The examiner further alleges that the notion of polypeptides which "comprise" an amino acid sequence, as recited in the original claims, is confusing because the additional element(s) implicated by "comprise" are not taught by the specification. Yet "comprise" is an accepted term in patent practice, with a well-defined meaning, and, contrary to the examiner's assertion, is <u>not</u> limited to process and pharmaceutical claims (see, for example, the appended excerpts from U.S. Patent Nos. 5,200,327, 5,200,339 and 5,212,071, attached as APPENDIX B).

Moreover, applicants' specification leaves no doubt as to what "comprising" means here. The application at page 14 sets forth additional elements contemplated by applicants, stating, for example, that autotaxin polypeptides can be "joined or linked to a variety of carrier proteins." Such a polypeptide clearly would "comprise" the autotaxin peptide and the carrier protein.

Accordingly, the use of "comprising" in the original claims is wholly consistent both with the applicable tenets of §112 and with what applicants regard as their invention. Nevertheless, in an effort to advance prosecution, applicants have employed "contains" in the amended claims, thereby implementing the suggestion of Examiner Celsa. *See also Ex parte Hankins*, 121 USPQ 151 (PTO Bd.Pat.App. 1958); *Ex parte Simpson*, 84 USPQ 299 (PTO Bd.Pat.App. 1949); *Ex parte Muench* 79 USPQ 92 (PTO Bd.Pat.App. 1948); *Ex parte Glycofreides*, 63 USPQ 242 (PTO Bd.Pat.App. 1944); ("comprising" and "containing" are synonymous for purposes of claim drafting). Withdrawal of this objection therefore is respectfully requested.

The examiner also has alleged a failure by the application to enable peptides bound to a "solid support," because the scope of such a solid support has not been defined. Applicants submit that the metes and bounds of a "peptide bound to a solid support" are well known in the art, and that additional description is not necessary to satisfy the requirements of 35 USC §112. As mentioned by the examiner, the term "solid support" encompasses such embodiments as affinity chromatography, carrier proteins, assay supports, *etc.*, which are well known in the art. The claims presented with this amendment no longer recite peptides bound to a solid support, and thus it is believed that this objection has been obviated.

Reconsideration and withdrawal of the rejections of claims 3-6 and 16-17 under 35 USC §112, first paragraph, are respectfully requested for the reasons set forth above.

35 USC §112, Second Paragraph Rejections

Applicants believe that most of the 35 USC §112, second paragraph rejections have been overcome by the presentation of new claims, however, the rejections are addressed below in order to provide a complete response to the Action.

Claims 3-6 and 16-17 stand rejected on the basis of the examiner's objection to the use of "comprising." While applicants believe that this language is clear, applicants have eliminated this term from the claims. Applicants request reconsideration and withdrawal of this rejection.

Claims 3, 5, 16 and 17 are rejected because they incorporate the phrase "an amino acid sequence corresponding to autotaxin." While applicants believe this recitation to be appropriate and unobjectionable, they have presented new claims to which the stated rationale for the rejection is not applicable. Reconsideration and withdrawal of the claims therefore are respectfully requested.

Claims 3 and 5 are rejected for reciting the term "at least five amino acids thereof." Again, while applicants do not concur with the examiner's reasoning, they have presented amended claims that omit the language in question and that otherwise meet the requirements of §112. Applicants therefore request that the examiner reconsider and withdraw this rejection.

Claims 5 and 17 are rejected for not prescribing how the polypeptides "are bound to a solid support." While applicants submit that the binding of proteins to a solid support is well

known in the art, the claims no longer recite polypeptides bound to a solid support, and reconsideration and withdrawal of this rejection is respectfully requested.

Claims 3-6 and 16-17 are rejected because the examiner believes that they must "define the physical characteristics of the [recited] polypeptide or protein." The claims are directed to autotaxin and certain fragments thereof. Contrary to the examiner's assertion, applicants have fully described the physical characteristics of autotaxin in the specification. Page 11 of the specification teaches that autotaxin has a molecular size of about 125 kDa and an isoelectric point of 7.7 ± 0.2. These physical characteristics, which the examiner has stated are missing from the description, coupled with the partial sequences disclosed in the specification, provide an ample description and characterization of the invention. Since the claims are not read in a vacuum, but must instead be interpreted according to the specification, the physical characteristics of autotaxin set forth in the specification are sufficient to define "autotaxin" as recited in the claims. Additionally, in order to advance the prosecution of this application, the newly presented claims have been written to recite physical characteristics of the claimed invention. Reconsideration and withdrawal of this rejection is thus respectfully requested.

Claims 5 and 17 are rejected for the use of the term "solid support." As stated above, this rejection has been obviated by the presentation of new claims which do not use this term, and withdrawal of this rejection is respectfully requested.

Claims 3 and 16 are rejected for being indefinite in the phrase "free of proteins with which it is naturally associated." The newly presented claims do not include this phrase, which is widely used in protein claims issued by the PTO (see, for example, the appended excerpts from U.S. Patent Nos. 5,192,538,

5,187,262 and 5,141,922, attached as APPENDIX C). Applicants submit that this rejection has been obviated, and they request its withdrawal.

Conclusion

In view of the foregoing amendments and remarks, this application is believed to be in condition for allowance, and an early indication of the same is respectfully requested.

It is believed that no additional fees are required; however, the Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 19-0741.

Respectfully submitted,

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Date

S. A. Bent
Stephen A. Bent
Reg. No. 29,768

FOLEY & LARDNER
Suite 500, 3000 K Street, N.W.
Washington, D.C. 20007-5109
(202) 672-5300